PATENT COOPERATION TREATY

From the:
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

BLAKE DAWSON WALDRON
PATENT SERVICES

RECEIVED: 05 JUL 2004

DATA ENTERED

PCT

WRITTEN OPINION
(PCT Rule 66)

To:

Blake Dawson Waldron
Level 39
101 Collins Street
MELBOURNE VIC 3000

Date of mailing *(day/month/year)*	05 JUL 2004
Applicant's or agent's file reference: DGC DAA 02 1355 7401	**REPLY DUE** within **TWO MONTHS** from the above date of mailing

International Application No.	International Filing Date *(day/month/year)*	Priority Date *(day/month/year)*
PCT/AU2003/001476	7 November 2003	7 November 2002

International Patent Classification (IPC) or both national classification and IPC
Int. Cl.[7] C12N 5/08, 5/10

Applicant
JOHNSON & JOHNSON RESEARCH PTY LIMITED et al

1. This written opinion is the **first** drawn by this International Preliminary Examining Authority.
2. This opinion contains indications relating to the following items:.

I	[X]	Basis of the opinion
II	[ ]	Priority
III	[ ]	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
IV	[ ]	Lack of unity of invention
V	[X]	Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
VI	[ ]	Certain documents cited
VII	[ ]	Certain defects in the international application
VIII	[X]	Certain observations on the international application

3. The **FINAL DATE** by which the international preliminary examination report must be established according to Rule 69.2 is:
7 March 2005

4. The applicant is hereby **invited to reply** to this opinion.

When? See the **Reply Due** date indicated above. However, the Australian Patent Office will not establish the Report before the earlier of (i) a response being filed, or (ii) one month before the **Final Date** by which the international preliminary examination report must be established. The Report will take into account any response (including amendments) filed before the Report is established.
If no response is filed by 1 month before the Final Date, the international preliminary examination report will be established on the basis of this opinion.
Applicants wishing to have the benefit of a further opinion (if needed) before the report is established should ensure that a response is filed at least **3 months before the Final Date** by which the international preliminary examination report must be established.

How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3.
For the form and the language of the amendments, see Rules 66.8 and 66.9.

Also For an additional opportunity to submit amendments, see Rule 66.4.
For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4*bis*.
For an informal communication with the examiner, see Rule 66.6.

Name and mailing address of the IPEA/AU	Authorized Officer
AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA E-mail address: pct@ipaustralia.gov.au Facsimile No. (02) 6285 3929	**GILLIAN ALLEN** Telephone No. (02) 6283 2266

WRITTEN OPINION

International application No.
PCT/AU2003/001476

I. Basis of the opinion

1. With regard to the **elements** of the international application:*

[X] the international application as originally filed.

[ ] the description, pages , as originally filed,
pages , filed with the demand,
pages , received on with the letter of

[ ] the claims, pages , as originally filed,
pages , as amended under Article 19,
pages , filed with the demand,
pages , received on with the letter of

[ ] the drawings, pages , as originally filed,
pages , filed with the demand,
pages , received on with the letter of

[ ] the sequence listing part of the description:
pages , as originally filed
pages , filed with the demand
pages , received on with the letter of

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language which is:

[ ] the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).

[ ] the language of publication of the international application (under Rule 48.3(b)).

[ ] the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the written opinion was drawn on the basis of the sequence listing:

[ ] contained in the international application in printed form.

[ ] filed together with the international application in computer readable form.

[ ] furnished subsequently to this Authority in written form.

[ ] furnished subsequently to this Authority in computer readable form.

[ ] The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

[ ] The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. [ ] The amendments have resulted in the cancellation of:

[ ] the description, pages

[ ] the claims, Nos.

[ ] the drawings, sheets/fig.

5. [ ] This opinion has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

** Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed"*

V. **Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Claims **1-65**	**YES**
	Claims	**NO**
Inventive step (IS)	Claims **None**	**YES**
	Claims **1-65**	**NO**
Industrial applicability (IA)	Claims **1-65**	**YES**
	Claims	**NO**

2. Citations and explanations

Citations

D1 WO 01/94944 A2 (MEMORIAL SLOAN-KETTERING CANCER CENTER) 13 December 2001

D2 Zeiling Cai et al. Transfected Drosophila cells as a probe for defining the minimal requirements for stimulating unprimed CD8+ cells. Proc Nat Acad Sci USA, 1996. 93:14736-41.

D3 WO 99/37313 A1 (GENZYME CORPORATION) 29 July 1999

D4 Lun Quan Sun et al. Resistance to human immunodeficiency virus type I infection conferred by transduction of human peripheral blood lymphocytes with ribozyme, antisense, or polymeric trans-activation response elements. Proc Nat Acad Sci USA, 1995. 92: 7272-76.

Novelty.

The prior at does not disclose a method of producing virus-specific CTLs that has all the features of the method of claim 1. Thus, all claims are novel.

Inventive Step.

The problem of present invention is to provide methods for producing cytotoxic T lymphocytes with activity against cells infected by specific viruses.

The solution provided in the present application is the provision of non-naturally occurring antigen presenting cells (nnAPCs), which are used to prime $CD8^+$ cells for virus-specific CTL activity. The nnAPCs of the examples of the description are admitted by the applicants to be known (see Example 1). The nnAPCs are loaded with viral peptide fragments comprising immunostimulatory epitopes that stimulate CTL activity. The antigens are presented to $CD8^+$ cells by incubating nnAPCs with $CD8^+$ cells in the presence of "supportive" cytokines.

The CTLs may also be transformed with a variety of virus inhibiting nucleic acids. The $CD8^+$ cells may be co-incubated with monocytes that present at least one antigen presented by the nnAPCs. The nnAPCs may also be used to prime $CD4^+$ cells and $CD34^+$ cells, which are co-administered with the virus-primed CTLs.

Continued in supplemental Box V

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

1. The claims are not clear

(i) Claim 10 is not clear. Adherent cells are a feature only of claim 3, not necessarily of claims 4-9.
(ii) Claim 12 is not clear. The term "the method of any one of claim 3" cannot be given a meaningful construction.
(iii) Claim 47 is not clear. Claim 38 does not mention adherent cells.

2 The claims are not fully supported by the description.

(i) The description only discloses nnAPCs produced from *Drosophila* cells. However, the term nnAPC of the claims is considered to encompass any non-naturally occurring or artificial antigen presenting cell.

(ii) The description only discloses nnAPCs that are loaded with antigenic peptides that they present to $CD8^+$ cells by incubation with the antigenic peptides. However, claim 1 encompasses any non-naturally occurring antigen presenting cell that presents specific viral antigenic peptides, however produced. It encompasses, for example, nnAPCs transformed with viral peptides.

(iii) In the examples of the description, the applicants have disclosed methods for making nnAPCs, loading such cells with known viral epitopes, and using them to activate virus-specific CTLS. They have disclosed further method steps, including incubation of CTLs with Il-2 and Il-7, transduction of CTLs with ribozymes, and further stimulation of CTLs with irradiated monocytes which have been pulsed with at least one virus-specific epitope.

However, the applicants have not disclosed that the nnAPCs have actually been made, or used to activate CTLs according to the methods of the claims. Nor have they disclosed actual production of CTLs transduced with ribozymes, or further activation of CTLs using irradiated monocytes. Since the cells have not been made, they have not been tested for any activity. Nor is the use of these CTLs to treat viral diseases disclosed. Claims to putative methods that are not disclosed as having been tested or shown to achieve the result to which they are directed can only be considered speculative .

NOTE. Claims 28-32, 37-65 are to methods of treatment of humans. The applicants are warned that, should this application proceed to National Phase, such claims may not be acceptable in all jurisdictions under the PCT.

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of Novelty and Inventive Step

Inventive Step (cont'd).

D1 and D2 both disclose nnAPCs and their use for presenting specific antigens to CTLs that enable the CTLs to specifically target cells displaying these antigens.

D1 discloses nnAPCs derived from mouse fibroblasts and discloses their use in methods of presenting antigens to activate cytotoxic T lymphocytes. Example 9 of the citation discloses nnAPCs engineered to express a flu viral peptide, and the use of such nnAPCs to prime cytoxic lymphocytes. It also discloses cells transformed with more than one antigen.

In so far as the claims are matter not disclosed in the citation, the following features are not considered to provide invention. It is not considered inventive to use known cytokines that have known stimulatory effects on CTLs. It is well known that CTLs can be primed by monocytes, as well as by dendritic cells, and there is no disclosure that any unexpected improvement is gained by this step, which is therefore not considered to provide invention. Similarly, the use of antigen presenting cells to prime helper T cells is well known, and not considered to provide invention.

Claims 1-3, 10-16, 35-40, 52-56, 60-65 lack invention over D1.

D2 discloses nnAPCs derived from *Drosophila* cells, and loaded with antigenic peptides to activate CTLs against specific target cells displaying the antigenic peptides. It is accepted that the citation does not specifically teach loading viral antigens onto the artificial antigen presenting cells. However, one skilled in the art would be aware that CTLs are active against virus-infected cells, and find it obvious to extend the methods of the citation to the production of antiviral CTLs.

Therefore, similarly to objections to the claims over D1, claims 1-3, 10-16, 35-40, 52-56, 60-65 lack invention over D2.

D3 discloses nnAPCs generated by fusing dendritic cells to cells expressing specific antigens. The cells are used to generate antigen specific CTLs. The CTLs may be transformed with ribozymes or antisense molecules. The citation teaches use of such cells against tumours. However, since it is well-known that CTLs are effective against virus-infected cells, the use of viral antigens instead of tumour antigens cannot be considered to provide invention to the present claims.

It is also accepted that nnAPCs generated from fusion of antigen expressing cells to dendritic cells are very different from nnAPCs generated from transforming *Drosophila* cells with HLA molecules. However, the claims are not limited to nnAPCS produced by any particular methods, and the APCs of the citation are certainly non-naturally occurring.

Similarly to objections in light of D1 and D2, and in so far as the nnAPCs of the claims encompass the artificial APCs of D3, all claims lack invention over D3.

D4 discloses transduction of human peripheral blood cells with antiviral ribozymes, to improve activity against virus infected cells. It is considered obvious to combine the teachings of D4 with those of D1 and D2, as all citations are specifically directed to producing T cells active against virus infections.

Therefore claims 4-9, 17-34, 41-51, 57-59 lack inventive step over D1 or D2 in light of D4.

It is noted that it is difficult to concede invention to method claims, even where they differ from methods of the prior art, where there is no disclosure that the claimed methods result in any unexpected improvement over the methods of the prior art.

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

1. The claims are not clear

   (i) Claim 10 is not clear. Adherent cells are a feature only of claim 3, not necessarily of claims 4-9.
   (ii) Claim 12 is not clear. The term "the method of any one of claim 3" cannot be given a meaningful construction.
   (iii) Claim 47 is not clear. Claim 38 does not mention adherent cells.

2 The claims are not fully supported by the description.

(i) The description only discloses nnAPCs produced from *Drosophila* cells. However, the term nnAPC of the claims is considered to encompass any non-naturally occurring or artificial antigen presenting cell.

(ii) The description only discloses nnAPCs that are loaded with antigenic peptides that they present to $CD8^+$ cells by incubation with the antigenic peptides. However, claim 1 encompasses any non-naturally occurring antigen presenting cell that presents specific viral antigenic peptides, however produced. It encompasses, for example, nnAPCs transformed with viral peptides.

(iii) In the examples of the description, the applicants have disclosed methods for making nnAPCs, loading such cells with known viral epitopes, and using them to activate virus-specific CTLS. They have disclosed further method steps, including incubation of CTLs with Il-2 and Il-7, transduction of CTLs with ribozymes, and further stimulation of CTLs with irradiated monocytes which have been pulsed with at least one virus-specific epitope.

However, the applicants have not disclosed that the nnAPCs have actually been made, or used to activate CTLs according to the methods of the claims. Nor have they disclosed actual production of CTLs transduced with ribozymes, or further activation of CTLs using irradiated monocytes. Since the cells have not been made, they have not been tested for any activity. Nor is the use of these CTLs to treat viral diseases disclosed. Claims to putative methods that are not disclosed as having been tested or shown to achieve the result to which they are directed can only be considered speculative .

NOTE. Claims 28-32, 37-65 are to methods of treatment of humans. The applicants are warned that, should this application proceed to National Phase, such claims may not be acceptable in all jurisdictions under the PCT.